REMARKS

Claims 224-292 are pending. By this Amendment, claims 224, 229 and 233 are amended. Reconsideration in view of the above amendment and following remarks is respectfully requested.

The courtesies extended to Applicants' representative by Examiner Saucier at the interview held June 10, 2004, are appreciated. The reasons presented at the interview as warranting favorable action are incorporated into the remarks below and constitute the record of the interview.

I. Claims 229 and 233 Satisfy the Requirements of 35 U.S.C. §112, First Paragraph

Claims 229 and 233 are rejected under 35 U.S.C. §112, first paragraph. Claims 229 and 233 are amended. Withdrawal of the rejection of claims 229 and 233 is respectfully requested.

II. The Claims Define Patentable Subject Matter

Claims 224, 228, 229, 232-245, 248-252, 255 and 258-266 are rejected under 35 U.S.C. 103(a) as unpatentable over WO 88/05261 to Owen; claims 246 and 247 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of WO 96/29864; claims 253 and 254 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of Chambers et al.; claim 257 is rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of Ingawall or WO 97/43899; claims 259-266 are rejected under 35 U.S.C. §103(a) as unpatentable over Owen in view of U.S. Patent No. 5,586,438 to Fahy; and claim 267 is rejected under 35 U.S.C. §103(a) as unpatentable over Owen and Fahy, and further in view of Tanner et al. These rejections are respectfully traversed.

The Examiner admits on page 4 of the June 15 Office Action that Owen does not disclose perfusing at least one organ with a first medical fluid at a first temperature wherein the first temperature is from about 12°C to about 24°C. Instead Owen discloses the first perfusion is performed at 37°C. However, the Examiner asserts that the recited temperature range is a mere optimization of ranges and thus is considered obvious. For at least the reasons set forth below, applicants respectfully disagree with the Examiner's assertion.

Temperature response in tissue hypothermia is not a simple matter of metabolism getting uniformly slower as the temperature is lowered. The sensitivity of reaction rates to temperature is diverse, for example, physical processes like diffusion have a simple linear rate response to temperature. Other processes like oxygen metabolism have an exponential response to temperature. Certain enzyme and membrane mechanisms have temperature thresholds, below which they essentially cease. Some biological macromolecules like fats have hypothermic phase transition temperatures below which they become more brittle.

The traditional approach to coping with this diverse temperature response has involved preserving in two main temperature domains. A first temperature domain is cold, and just above freezing, about 4°C, where reaction rates are minimized beneficially and detrimentally. At these low temperatures, cell deterioration proceeds but at a very slow rate, and the deterioration is reversible even after many days cold storage, in some cases.

A second temperature domain is at about 37°C. At this temperature, all metabolic functions operate at a normal rate and so the preserved organ stays normal, as long as its supply and waste removal needs are met. However, with existing technology, the supply and waste removal requirements are so dynamic that to date a practical system has not yet been developed that thoroughly meets this need for more than 4 to 24 hours. As a consequence, preservation at this temperature has not found any clinical application.

As a consequence, applicants respectfully submit that it is significant to make targeted duration preservations at specific temperatures, that allow specific metabolic results to come to pass while preventing others. An example would be the tissue pH homogeneity that is achieved at about 20°C.

Although the true activity level of mitochondria in organ preservation below 20°C is difficult to describe, preserving at a targeted temperature from about 12°C to 24°C takes advantage of reduced or arrested mitochondrial activity. That is, at all hypothermic temperatures down to near freezing, consumption of glucose and the production of lactate by the cells (although at slower rates as the cells cool), can be documented and further shows that the glucose-pyruvate-lactate pathway is active and producing ATP. This pathway does occur in the cytosol, outside the mitochondria, indicating that beneficial energy stores production is continuing despite mitochondrial inactivity.

Anaerobic mitochondrial activity (as would occur in hypothermia without oxygen) is considered to be potentially damaging to the cell in that it may cause the release of oxygen-derived free radicals into the cell, which are the main suspect for damage in ischemia-reperfusion injury. Therefore, finding a way to produce ATP in the cells without involving the mitochondria, can provide beneficial effects.

Further, the discontinuities in Arrhenius plots, e.g. documented for the effect of temperature on ADP-stimulated respiration in mitochondria for 4 species, confirm that the effects of hypothermia are NOT predictable on the basis of assuming a linear retardation of metabolism and cooling. The discontinuities are generally interpreted, on the basis of a Lyons-Raison hypothesis, to represent changes in membrane characteristics that cause unpredictable metabolic imbalance and provide one component of injury sustained by homeothermic cells during cold exposure.

Moreover, applicants respectfully submit that it has been demonstrated that the Arrhenius plot of inactivation (killing) rates of cells exposed to reduced temperatures changes slope in the region of 8-10°C. This is representative of distinct mechanisms of hypothermic inactivation above and below these transition temperatures. On this basis there could be distinct advantages of storing organs above the aforementioned transitions, for example above 15°C, that is not predicted by the classical single rate limiting process.

Accordingly, applicants respectfully submit that storage of homeothermic organs in the temperature range above these transitions, for example about 12°C to about 24°C, represents a novel and non-obvious approach to avoiding additional mechanisms of injury that would be sustained by cooling organs, for example, below this transition range. Furthermore, these additional mechanisms of injury are not predicted by classical Arrhenius kinetics.

In addition to the above discussed arguments, applicants additionally submit that it would not have been obvious to one or ordinary skill in the art to modify the teaching of Owen. That is, the systems and methods of Owen are designed to maintain the appropriate temperature, pressure, oxygen concentration and ph of the nutrient fluid. For example, as discussed on page 20 of Owen, the acceptable ranges for temperature of perfusate for an organ are normothermic 37°C +/- 1°C and hypothermic temperature 4°C to 6°C. There are two circuits in the apparatus of Owen, one for cooling the electrolyte perfusion below 10°C and the other for maintaining the emulsion perfusion at 37°C. The electrolyte perfusion solution is cooled from refrigerant coils immersed in reservoir 4 and hydrostatic reservoir 7. Fluid passing through the circuit can also be directed into reservoir 6 containing the emulsion perfusion, to cool the temperature of the perfusion if it exceeds 37°C. Sustaining the emulsion perfusion at 37°C is maintained by heating coils immersed in reservoir 3 and thermal regulator 5.

Thus, the apparatus of Owen is concerned with maintaining the temperatures of the fluids at "acceptable ranges". As such, Owen merely discloses perfusing at a normothermic temperature at 37°C +/- 1°C. Owen does not teach, disclose or even suggest perfusing the at least one organ with a first medical fluid at a first temperature to at least one of maintain and restore pre-ischemia or pre-hypoxia energy levels in the organ, wherein the first temperature is from about 12°C to about 24°C.

None of the other cited art makes up for the deficiencies of Owen discussed above.

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §103 is respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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WPB:KMM/jfb

Attachment:
Petition for Extension of Time

Date: **October 15, 2004**

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